UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JOSEPH D. ROSENBLATT,
PIA CHALLITA-EID,
SHERIE MORRISON,
CAMILLE N. ABBOUD, and
SEUNG-UON SHIN

Appeal No. 2004-1505
Application No. 09/016,743

ON BRIEF

Before WILLIAM F. SMITH, ADAMS, and GREEN, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 3-10, and 25.

Claim 1 is representative of the subject matter on appeal and read as follows:

1. A chimeric molecule suitable for stimulating a tumor specific immune response comprising:

a complete antibody having heavy and light chains each with an N terminus and being capable of specifically binding to a tumor cell associated antigen, and

a chemokine, which is coupled to the N terminus of the heavy or light chain of the antibody such that the antibody remains capable of binding to the tumor cell associated antigen and the chemokine retains activity.

The references relied upon by the examiner are:

Bacus	5,514,554	May 7, 1996
Hölzer et al.	5,824,782	Oct. 20, 1998

Huston et al. (Huston), "Protein Engineering of Single-Chain Fv Analogs and Fusion Proteins," Methods in Enzymology, Vol. 203, pp. 46-88 (1991)

Claims 1, 3-8, 10, and 25 stand rejected under 35 U.S.C. § 103(a). The examiner relies upon Hölzer and Huston as evidence of obviousness. Claims 1 and 9 are rejected under 35 U.S.C. § 103(a) with the examiner relying upon Huston, Hölzer, and Bacus as evidence of obviousness. In addition, claims 1, 3-10, and 25 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite and 35 U.S.C. § 112, first paragraph (written description).

We affirm the prior art rejections and reverse the rejections under 35 U.S.C. § 112, first and second paragraphs.

Discussion

1. Rejections under 35 U.S.C. § 112, first and second paragraphs.

The issue raised in both of these rejections involves the requirement of claim 1 that a "complete antibody" be used. Under the second paragraph of this section of the statute, the examiner indicates that it is not clear whether this phrase means "'complete' in a sense of binding or having the function of the antibody such as binding or Fc mediated function, or does the antibody comprise a constant region of CH1, CH2, and CH3?" Examiner's Answer, page 12. Under the written description requirement of this

section of the statute, the examiner questions whether the specification describes a "complete antibody." Id., page 14.

In amending claim 1 to recite a "complete" antibody, appellants introduced perhaps needless confusion into the record since the specification does not appear to use the phrase "complete antibody." Rather, antibodies as used in the present invention are defined as follows:

> The term 'antibodies' as used herein refers to various types of immunoglobulin, including IgG, IgM, and IgA, and their relevant subclasses. The antibodies may be monoclonal or polyclonal and may be of any species of origin, including (for example) mouse, rat, rabbit, horse, or human, or may be chimeric antibodies, and include antibody fragments such as, for example, Fab, $F(ab')_2$, and Fv fragments, and the corresponding fragments obtained from antibodies other than IgG.

Specification, paragraph bridging pages 22 and 23.

Thus, appellants indicate in the original disclosure of this application that antibodies used from the present invention may be antibodies that may be aptly characterized as "whole," "intact," "complete," or "entire" or antibody fragments such as Fab, $F(ab')_2$, and Fv fragments. Appellants argue "since the term 'antibodies' is defined as including whole antibodies like IgG, IgM, and IgA, as well as fragments, it is apparent that the phrase 'complete antibody' means complete in the sense of having a complete structure, i.e. an antibody structure having VH and VL domains as well as constant regions CH1, CH2 and CH3." Examiner's Answer, page 13, first paragraph.

The examiner does not dispute that the original disclosure of this application describes "whole" antibodies as well as fragments thereof. Nor has the examiner established that one of ordinary skill in the art would have difficulty in understanding the difference between a "whole" or "complete" antibody and a fragment thereof. As we

view the record, appellants have chosen to restrict their invention to the embodiment that includes a whole or complete antibody as opposed to the embodiment which involves fragments of antibodies. With this understanding, we do not find the claims indefinite, nor do we find that the claims violate the written description requirement of 35 U.S.C. § 112, first paragraph.

The rejections under 35 U.S.C. § 112, first and second paragraphs, are reversed.[1]

2. Rejections under 35 U.S.C. § 103.

Appellants state that "dependent claims 3-10 and 25 stand or fall with the independent claim from which they depend." Appeal Brief, page 6. Accordingly, in considering the issues raised under the rejection under 35 U.S.C. § 103(a) which is based upon Hölzer and Huston, we shall limit our consideration to claim 1 on appeal. See the then existing provisions of 37 CFR § 1.192(c)(7).

The chimeric molecule of claim 1 has two parts. The first part is a complete antibody having heavy and light chains each with an N-terminus and being capable of specifically binding to a tumor cell associated antigen. The second part is a chemokine coupled to the N-terminus of the heavy or light chain of the antibody. The complete antibody and chemokine are coupled in such a manner that the antibody remains capable of binding to the tumor cell associated antigen and the chemokine retains it activity.

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[1] In the future, such confusion would be avoided if appellants would comply with and/or the examiner would enforce the requirements of 37 CFR § 1.75(d)(1).

There is no real dispute as to what Hölzer and Huston describe. Rather, appellants and the examiner disagree on what conclusion should be reached from a consideration of the two disclosures.

Hölzer describes a complete antibody having heavy and light chains each with an N-terminus and being capable of specifically binding to a tumor cell associated antigen. See, e.g., column 3, lines 22-26. The complete antibody of Hölzer is coupled to a chemokine, e.g., IL-8. Id. However, the chemokine of Hölzer is coupled to the C-terminus of the complete antibody, not the N-terminus as required by claim 1 on appeal. See, e.g., the third construct illustrated in Fig. 1 of Hölzer.

Hölzer states that the biological activity of IL-8 is associated with the N-terminal portion of the molecule. Id., column 7, lines 41-51. Thus, in forming the chimeric molecules of that invention, the question arose as to whether coupling the N-terminal portion of the IL-8 molecule to the C-terminal portion of the complete antibody would abrogate the biological activity of IL-8. Hölzer avoided the possibility of this problem by providing linker peptides between the C-terminal of the complete antibody and the N-terminal portion of the IL-8 molecule. Id.

Huston describes chimeric molecules formed of single-chain Fv antibody fragments and proteins that are denominated as effector proteins. Huston, page 48. The single-chain Fv fragment "forms the entire antibody combining site." Id., page 47. A fusion protein comprising a single-chain Fv fragment and an effector protein is of interest in in vivo diagnostics and therapeutics. Id., page 48. Of particular interest is Huston's discovery that effector proteins can be attached to either the N-terminus or the C-terminus of the single-chain Fv fragment with the resulting fusion protein retaining the

binding properties of the Fv antibody fragment. See, e.g., Figure 3 and page 57 of Huston.

We agree with the examiner's conclusion that it would have been obvious to a person of ordinary skill in the art at the time of the present invention to "have made a construct comprising a binding domain which specifically binds to a tumor cell associated antigen and a chemokine fusion as taught by Holzer et al with the chemokine linked to the amino terminus of the heavy chain as taught by Huston et al." Examiner's Answer, page 4. In viewing the two references together, we conclude a person of ordinary skill in the art would have had a reasonable expectation of success in forming a chimeric molecule comprising a complete antibody capable of binding to a tumor cell associated antigen and a chemokine where the chemokine is coupled to the N-terminus of the heavy or light chain of the complete antibody with the chimeric molecule being capable of binding to the tumor cell associated antigen and retaining the chemokine activity.

Hölzer and Huston provide ample motivation to create chimeric molecules that bind a tumor cell associated antigen and possess chemokine activity. It is not clear on this record why Hölzer created that chimeric molecule with the chemokine being coupled to the C-terminus of the complete antibody rather than the N-terminus as required by claim 1 on appeal. It may be that Hölzer was concerned about retaining the ability of the complete antibody to bind to the tumor cell associated antigen or perhaps prior art reasons dictated Hölzer working at the C-terminus of the complete antibody instead of the N-terminus.

Regardless, Huston provides evidence that at the time of the present invention persons of ordinary skill in this art understood that effector proteins can be attached to either the N-terminus or C-terminus of a single-chain Fv fragment with the resulting chimeric molecule retaining its binding activity. Viewing the two references together, it is seen that a person of ordinary skill in the art would have understood at the time of the present invention that an alternative to the embodiment described in Hölzer would be to couple the chemokine, e.g., IL-8, to the N-terminus of the complete antibody. In so doing, one would remove any concern of abrogating the biological properties of IL-8 because its N-terminus would not be affected. In the event that such a construct would raise a question as to whether the binding ability of the complete antibody would be affected, such concerns are allayed by Huston's disclosure that effector proteins can be bound to the N-terminus of Fv antibody fragments with the resulting chimeric molecule retaining its antibody binding property.

Appellants rely upon the declaration of Dr. Seung-Uon Shin filed under 37 CFR § 1.132 in rebuttal of the obviousness rejection of claim 1. The premise of Dr. Shin's declaration is that "there are significant differences with regard to the avidity, half-life, and chemokine carriage which would cause scientists skilled in the field of antibody cancer therapeutics to avoid adapting single chain Fv analog technology to whole antibody cancer therapeutics." Shin declaration, para. 4.

Dr. Shin relies upon various documents in the declaration. However, we do not find copies of the relied upon documents in the Image File Wrapper (IFW). Furthermore, some of the documents relied upon by Dr. Shin are stated to have publication dates subsequent to the filing date of this application. The relevance that

such documents would have in determining what would have been obvious to a person of ordinary skill in the art at the time of the present invention is not apparent. Be that as it may, we have considered Dr. Shin's declaration on the basis that the facts are as stated but do not find that it is a sufficient rebuttal of the obviousness rejection.

At best, Dr. Shin's declaration sets forth the considerations a person of ordinary skill in the art would have in determining whether a chimeric molecule that is to bind to a tumor cell associated antigen should be premised upon a complete antibody or a single-chain Fv fragment. Clearly, there are pros and cons for using each type of antibody moiety. In fact, a person following the teachings of Hölzer would face the same considerations since Hölzer states that the antibody portion of that chimeric molecule may be a complete antibody as required by claim 1 on appeal or an antibody fragment including a single-chain Fv fragment as in Huston. See the constructs illustrated in Fig. 1 of Hölzer. Thus, the considerations set forth by Dr. Shin in the declaration are only those that one seeking to implement the disclosure of Hölzer would have. Presumably a person of ordinary skill in the art at the time of the present invention would have had sufficient skill in order to make an informed decision as to whether a chimeric molecule according to Hölzer should be based upon a complete antibody as claimed or a single-chain Fv fragment. The Shin declaration does not address the main issue in this rejection, i.e., whether it would have been obvious to couple IL-8 to the N terminus of the antibody of Hölzer, rather than the C terminus with a reasonable expectation of successfully obtaining a chimeric molecule that will bind to a tumor associated antigen and possess IL-8 activity.

In regard to the separate rejection of claims 1 and 9 on the basis of Huston, Bacus, and Hölzer, we note that appellants rely upon the same arguments made in regard to the previously discussed rejection under 35 U.S.C. § 103. Appeal Brief, pages 12-13. Accordingly, we affirm both obviousness rejections.

The decision of the examiner is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

William F. Smith
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

Lora Green
Administrative Patent Judge

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